

Thiourea catalysis of NCS in the synthesis of β -chloroethers

Paul A. Bentley*, Yujiang Mei, Juan Du

Department of Chemistry and Chemical Biology, MSC03 2060, University of New Mexico, Albuquerque, NM 87131-0001, USA

Received 14 December 2007; revised 7 February 2008; accepted 7 February 2008

Available online 13 February 2008

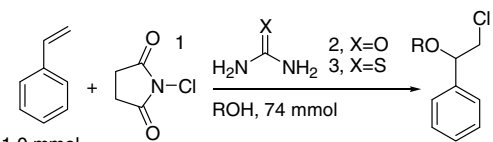
Abstract

Thiourea catalysis of olefin chlorination with NCS in an alcohol gives β -chloroethers with a very fast reaction of high yield.
© 2008 Published by Elsevier Ltd.

Organocatalysts allow environmentally friendly catalysis in a number of synthetic transformations.¹ The organocatalytic properties of urea were initially applied to sulfoxide allylation² and Claisen rearrangement,³ but has since seen as an expanded role.^{4–19} However, the synthesis of β -chloroethers by chlorination remains unexplored. Non-organocatalytic methods to prepare β -chloroethers with an alcohol^{20–37} have failed to achieve a product in high yield at a very rapid rate.

Our studies have embraced catalyzed chlorination with *N*-chlorosuccinimide (NCS, **1**). We have demonstrated the synthesis of halohydrin with water and NCS catalyzed by thiourea.³⁸ Subsequently, a broader profile of reactions was sought for this technique. The reaction of NCS with styrene in methanol provided the β -chloroether in very poor yield after a long time (Table 1, entry 1). Like the halohydrin synthesis,³⁸ urea (**2**) offered no significant catalytic advantage when β -chloroethers were formed, with only a marginal improvement in yield (Table 1, entry 2). By contrast, thiourea (**3**) allowed the very fast chlorination of styrene with very good yield and complete regiocontrol (Table 1, entry 3). The amount of thiourea was diminished to 5 mol % to afford a more slowly converted reaction; but with a notably improved yield (Table 1, entries 4 and 5). However, even lower levels of catalyst were detrimental to the reaction's performance (Table 1, entry 6). Less NCS gave a slower reaction and lower yield (Table 1,

Table 1
Optimized catalysis of olefin chlorination



Entry	R, Temp. (°C)	Catalyst (mol %)	NCS (mmol)	Time	Yield (%)
1	Me, 23	—	0	96 h	33
2	Me, 23	2	20	96 h	48
3	Me, 23	3	20	10 min	85
4	Me, 23	3	10	15 min	91
5	Me, 23	3	5	30 min	96
6	Me, 23	3	2	96 h	78
7	Me, 23	3	5	45 min	83
8	Me, 23	3	5	96 h	61
9	Et, 23	3	5	3 h	75
10	ⁱ Pentyl, 23	3	5	24 h	53
11	^t Bu, 28	3	5	24 h	44
12	Ph, 42	3	5	4 h	45 ^a

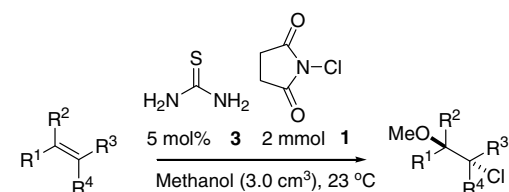
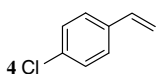
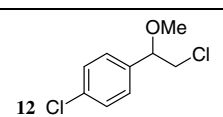
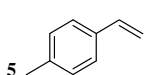
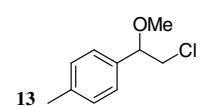
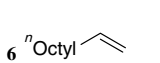
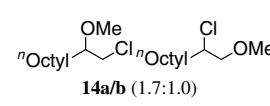
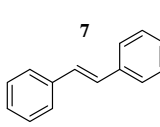
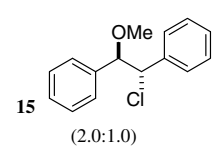
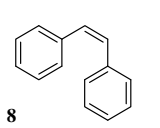
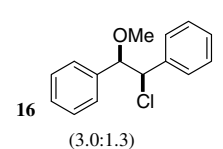
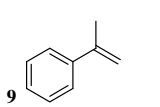
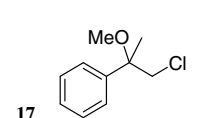
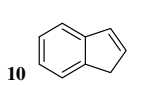
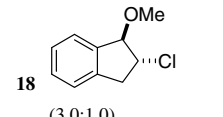
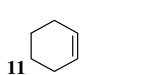
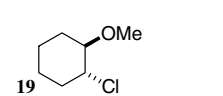
^a 1.7:1.0 Ratio of regioisomers.

entries 7 and 8). Economy, reaction speed and yield were evaluated when conditions were selected as optimal (Table 1, entry 7).

Next, the alcohol was varied and the effect on the reaction observed. Methanol replacement with ethanol (Table 1, entry 9) reduced the reaction rate with a slightly lower yield. At a higher temperature, phenol also reacted with similar speed, but afforded the β -chloroether in only moderate yield (Table 1, entry 12). However, chlorination in

* Corresponding author. Tel.: +1 505 277 0369; fax: +1 505 277 2609.
E-mail address: pabco21@gmail.com (P. A. Bentley).

Table 2
A variety of alkenes chlorinated with NCS

				
Entry	Olefin, solvent	Chloroether ^a	Time (min)	Yield (%)
1			90	94
2			120	95
3		 14a/b (1.7:1.0)	15	100
4		 (2.0:1.0)	15	95
5		 (3.0:1.3)	15	98
6			5	94
7		 (3.0:1.0)	90	83
8			15	56

^a Ratios determined by ¹H NMR.

pentan-3-ol or *t*-butanol gave a much slower reaction with only moderate yield (Table 1, entries 10 and 11) despite an elevated temperature. Overall bulkier alkyl/aryl (R) functionality gave reduced reaction rate and yield, probably due to steric hindrance, although reactions would be improved with more catalysts or NCS.

Ultimately, styrene was replaced with alternative olefins and the modified substrate's influence upon the reaction was investigated.

Monosubstituted olefins with various electronic environments were studied initially with the replacement of

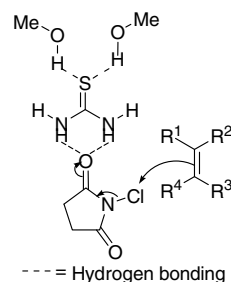


Fig. 1. Speculated key step in the catalytic process.

the proton at the *para* position of styrene with a halogen (Table 2, entry 1) that provided a slower reaction with a higher yield. A similar proton replacement with a methyl group caused an even slower reaction (Table 2, entry 2). The phenyl group of styrene was replaced with an aliphatic functionality that gave a faster reaction rate and an excellent yield of the β -chloroethers (Table 2, entry 3) with a loss of regioselectivity. Subsequently, disubstituted olefins were scrutinized with the reaction of stilbene (7 or 8) that provided a significantly faster reaction than styrene and noticeably higher yield (Table 2, entries 4 and 5). However, digeminal substituted olefin 9 offered the fastest reaction with a very good yield (Table 2, entry 6). Next, cyclic olefins were explored and provided variable results. Indene (10) reacted more slowly than styrene but with identical yield. However, cyclohexene 11 gave a faster reaction than styrene with complete stereocontrol in a moderate yield. In general, excellent regioselectivity was demonstrated in a wide range of substrates (except 6) and the reactions were achieved rapidly and in good yield.

In light of the propensity of thiourea to hydrogen bond with carbonyls³⁹ and the capacity for reactions with *N*-halosuccinimides to be catalyzed by Brønsted acids,⁴⁰ we speculate that a key step in the mechanism may include hydrogen bonds between amidic oxygen and thiourea protons as shown in Figure 1.³⁸ Polar protic solvents may provide an extended and strong hydrogen bond network.

Thiourea is adept at the catalysis of NCS reactions and affords the fastest chlorination of alkenes to give β -chloroethers with excellent yields. To optimize conditions, the influence on the reaction of different amounts of NCS and thiourea has been discerned. A diverse array of olefins and a number of alcohols, including very effective primary alcohols, have been shown to be applicable to the technique. Further thiourea catalyzed NCS chlorinations are under investigation and NBS has shown some distinctly different facets in the way it interacts with thiourea that are currently under further examination. An enantiopure derivative of thiourea is being designed to afford asymmetric reactions.

Acknowledgements

Financial support from the Department of Chemistry and Chemical Biology and the Research Allocation

Committee, University of New Mexico, is gratefully acknowledged.

Supplementary data

Experimental procedures with ^1H and ^{13}C NMR spectra for all products are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.040.

References and notes

1. Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH, 2004.
2. Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259.
3. Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647.
4. Further reactions using thiourea catalysts include Diels–Alder, 1,3-dipolarcycloaddition, nitron TMSCN addition, Strecker, Mannich, aza-Henry, hydrophosphonylation, Pictet–Spengler, Michael addition, Baylis–Hillman and reductive amination reactions.
5. Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217.
6. Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817.
7. Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
8. Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
9. Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191.
10. Yoon, T. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 466.
11. Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102.
12. Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.
13. Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Chem. Pharm. Bull.* **2004**, *52*, 477.
14. Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.
15. Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967.
16. Manher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301.
17. Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589.
18. Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293.
19. Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* **2006**, *8*, 741.
20. Methods for the synthesis of β -chloroether include hypervalent iodine reagents, hypochlorous acids and hypochlorites reactions, $\text{NaIO}_4/\text{NaCl}$, phenylselenyl chloride, nitrobenzenesulfonyl peroxide and tetraethylammonium chloride, electrolysis with sodium chlorides, chlorine, *N*-methylmorpholine-*N*-oxide/cyanuric chloride, Pd(II) -complex/ CuCl_2 , trichloroisocyanuric acid and *N*-chlorosaccharins.
21. Yusubov, M. S.; Drygunova, L. A.; Zhdankin, V. V. *Synthesis* **2004**, 2289.
22. Yusubov, M. S.; Yusubov, R. J.; Filimonov, V. D.; Chi, K.-W. *Synth. Commun.* **2004**, *34*, 443.
23. Yusubov, M. S.; Yusubova, R. Y.; Filimonov, V. D.; Ki-Wan, C. *Russ. J. Org. Chem.* **2002**, *38*, 902.
24. Boguslavskaya, L. S. *Russ. Chem. Soc. Rev.* **1972**, *41*, 740.
25. Heasley, V. L.; Gipe, R. K.; Martin, J. L.; Wiese, H. C.; Oakes, M. L.; Shellhamer, D. F. *J. Org. Chem.* **1983**, *48*, 3195.
26. Shellhamer, D. F.; Gipe, R. K.; Wiese, H. C.; Oakes, M. L.; Heasley, G. E. *Tetrahedron Lett.* **1980**, *21*, 4133.
27. Beger, J.; Jacobi, R.; Storch, A.; Ullmann, M. *J. Prakt. Chem.* **1980**, *322*, 294.
28. Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501.
29. Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D. *Tetrahedron* **1988**, *44*, 2261.
30. Yoshida, M.; Mochizuki, H.; Suzuki, T.; Kamigata, N. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3704.
31. Shinoda, K.; Yasuad, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4393.
32. Schmidt, E. K. G.; Wiese, W. *Tetrahedron Lett.* **1980**, *27*, 4425.
33. Elinson, M. N.; Makhova, I. V.; Nikishin, G. I. *Ser. Khim.* **1990**, 125.
34. Rosenau, T.; Potthast, A.; Kosma, P. *Tetrahedron* **2002**, *58*, 9809.
35. El-Qisairi, A. K.; Qaseer, H. A.; Henry, P. M. *J. Organomet. Chem.* **2002**, *656*, 168.
36. Mendonca, G. F.; Sanseverino, A. M.; de Mattos, M. C. S. *Synthesis* **2003**, 45.
37. de Souza, S. P. L.; da Silva, J. F. M.; de Mattos, M. C. S. *J. Braz. Chem. Soc.* **2003**, *14*, 832.
38. Bentley, P. A.; Mei, Y.; Du, J. *Tetrahedron Lett.* **2008**, *49*, 1425.
39. Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299.
40. Veenman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1334.